Peritoneal Cancer and Occupational Exposure to Asbestos: Results From the Application of a Job-Exposure Matrix

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Background *Because of the rarity of peritoneal mesothelioma, occupational risks associated with it have seldom been studied, particularly among women. In this respect, death certificates databases may provide numbers large enough for analysis, although the International Classification of Diseases, 9th revision (ICD-9) does not single out mesothelioma from the rest of peritoneal cancers. The aim of this paper is twofold: to explore occupational risks of peritoneal cancer among men and women, and to test the performance of a job-exposure matrix in detecting its association with asbestos exposure using the occupation and industry reported in the death certificate.*

Methods *From a large database containing information on the 1984–1992 death certificates of 24 U.S. states, we identified 657 deaths from peritoneal cancer and 6,570 controls who died from non-malignant diseases, 1:10 matched by region, gender, race, and 5-year age group.*

Results *Occupations at risk included insulators among men, and machine operators among women. Among men, we found a significant increase in risk associated with employment in manufacturing industries, such as industrial and miscellaneous chemicals; miscellaneous non-metallic mineral and stone products; construction and material handling machines; and electrical machinery, equipment, and supplies; as well as in services to dwellings and other buildings. Industries at increased risk among women included elementary and secondary schools; miscellaneous retail stores; and publishing and printing. Our job-exposure matrix classified 17 male cases and 3 controls in the high probability category of exposure to asbestos (OR = 61.6). Among men, risk of peritoneal cancer increased significantly by probability and intensity of exposure to asbestos. No such pattern was observed among women. The job-exposure matrix did not classify any female subjects in the high probability or intensity of asbestos exposure.*

Discussion *This study provides evidence that death certificate data and job-exposure matrices are useful tools to observe well-established associations, such as the one existing between peritoneal cancer and asbestos exposure among men, in spite of crude information, disease misclassification, and occupational misclassification. These factors are more likely to preclude meaningful results among women.* Am. J. Ind. Med. 35:9–14, 1999. *Published 1999 Wiley-Liss, Inc.*†

KEY WORDS: peritoneal cancer; asbestos; insulation workers; epidemiology; job-exposure matrices

INTRODUCTION

Malignant mesothelioma arises from the lining cells of the coelomic cavities [Mack, 1995]. Malignant mesotheliomas of the pleura and the peritoneum share exposure to asbestos as the major etiologic factor [Spirtas et al., 1994].

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However, they differ in respect to sex-ratio, route of exposure (inhalation vs. ingestion) [Mack, 1995], and fiber type (chrysotile vs. amosite asbestos) involved [Peto et al., 1995; Ribak et al., 1989]. In contrast with pleural mesothelioma, which predominates among men, mesothelioma of the peritoneal cavity occurs with roughly equal frequency in men and women [Mack, 1995]. This could imply that the pertinent exposure is distributed with little reference to gender. The geographical pattern of peritoneal mesothelioma in the United Kingdom parallels the past distribution of the asbestos industry, but unlike pleural mesothelioma, it did not cluster in seaports where shipbuilding and ship repairing were carried out [Gardner et al., 1985]. The contrasting features of peritoneal and pleural mesothelioma suggest that different routes of exposure to asbestos and/or different fiber types may contribute to distinct epidemiologic patterns [Leigh et al., 1991].

The underlying cause of death in death certificates is coded using the International Classification of Diseases, 9th revision (ICD-9), which does not single out mesothelioma from the rest of peritoneal cancers. Besides, the proportion of mesothelioma among all peritoneal tumors is unclear. In a recent review of SEER incident data, cancer of the peritoneum was only considered jointly with cancer of the retroperitoneum [Mack, 1995]. Mesothelioma accounted for about 20% of these two cancer sites combined and it did not vary by gender. However, the proportions of epithelium-derived cancers (including mesothelioma) and connective and other soft tissue-derived cancers might be different between the peritoneum and the retroperitoneum. Nevertheless, a recent study in the United Kingdom showed that mortality from asbestosis was more closely related to that from peritoneal cancer than pleural cancer [Coggon et al., 1995], which supports using mortality data to explore the association between asbestos exposure and peritoneal cancer. The same report showed that the risks for cancers of the pleura and peritoneum distribute quite differently by occupation, with construction workers being at much higher risk for peritoneal cancer than pleural cancer, vehicle body builders and plumbers showing excesses at both sites, and various other occupations, such as metal plate workers, upholsterers, electricians, and welders showing only pleural cancer excesses [Coggon et al., 1995].

To further investigate the association of peritoneal cancer and occupational exposure to asbestos by gender and to explore the reliability of both a priori designed job-exposure matrices and occupational information in the death certificate, we conducted a case-control study using data from a national surveillance program of occupational diseases developed since 1984 by the National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics [Burnett and Dosemeci, 1994]. We first designed a job-exposure matrix based on the 1980 U.S. Census list of occupations and industries, and subsequently applied it to the codes on the death certificates of cases and controls.

METHODS

Since 1984, the National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics have supported the coding of occupation and industry titles on death certificates from a number of U.S. states according to the 1980 U.S. Census occupation and industry codes [Burnett and Dosemeci, 1994]. Briefly, it currently consists of a total of 4.5 million death certificates from 24 U.S. states, covering the years 1984–1992. Only one occupation and industry combination is reported for every subject, and no duration of employment is available. Data reported on the death certificates of subjects aged 20 years or more were used to evaluate the risk of peritoneal cancer associated with occupational exposure to asbestos by gender. Cases were 657 subjects (249 men and 408 women) who died from cancer of the peritoneum (ICD-9 codes 158.8 and 158.9). Eighteen men and 20 women were African-American. Because of even smaller numbers, subjects of Asian origin and native Americans were excluded from the analysis. All the remaining were noted as Whites in the death certificate. Ten controls per case were selected from among subjects who died from non-malignant diseases, frequency-matched to cases by geographic region, race, gender, and 5-year age group.

Risk of peritoneal cancer was first explored by industry and occupation. To evaluate risk in relation to occupational exposure to asbestos, we designed a job-exposure matrix based on the 1980 U.S. Census list of occupations and industries, and subsequently applied it to the occupation and industry codes in the death certificates of cases and controls. An estimate of intensity (none = 0, low = 1, medium = 2, high = 3) and probability (none = 0, low = 1, medium = 2, high = 3) of exposure to asbestos was developed for each 3-digit occupation and industry code. Intensity of exposure was estimated based upon literature information [Parmeggiani, 1985], computerized databases (OSHA files, NIOSH inspection data base), unpublished industrial hygiene reports, and personal experience. The probability index associated with a given occupation or industry 1980 Census code was estimated based on the proportion of exposed workers within the job title or industry under consideration, and the number of other occupations or industries coded likewise. In addition, occupations were characterized into two groups depending upon the sources of exposure. If exposure was determined by the occupation itself regardless of industry (e.g., insulators), final intensity and probability scores were obtained by squaring the respective occupational levels. If exposure was determined by both occupation and industry (e.g., maintenance workers in shipyards), intensity and probability scores resulted from multiplying the respective levels of occupation and industry. The final scores of probability and intensity of exposure were further grouped in four categories (none = 0, low = 1–2, medium = 4, high (6). Cut points were selected a priori, with the highest category defined by a score of 6 to increase the statistical power. As excluding any probability of exposure to asbestos was possible only for 1.5% of the study population (70/7227), due to the widespread use of asbestos in the past, the unexposed reference group included also subjects with low probability and low intensity exposure in order to provide more stable risk estimates.

Odds ratios (ORs) were estimated by logistic regression and 95% confidence intervals (95% C.I.) by the Wald method using the GMBO program in the Epicure software package [Preston et al., 1990]. Covariates in the logistic regression model included age (continuous), marital status (never married versus ever married), socio-economic status (five categories, based on the Green's score for specific occupations [Green, 1970]), metropolitan vs. non-metropolitan residence, and ethnic origin (North America and Europe vs. South America and Africa). The statistical significance of the linear trend by increasing intensity and probability of exposure to asbestos was tested by dividing the regression coefficients of the variables assumed as non-categorical by their standard error to generate a Z statistic. Under the null hypothesis, this test behaves as a normal standard deviate [Breslow and Day, 1980]. Two-tailed *p* values were considered throughout this article.

TABLE I. Occupations and Industries With at Least 3 Cases Associated With an Increase in Risk of Peritoneal Cancer (OR $\geq$ 1.5): Study of Death Certificates in 24 U.S. States, 1984–1992

Census code	Occupation or industry title	Cases/controls	OR (95% C.I.)
Men			
Occupations			
549	Not specified mechanics and repairers	3/14,	1.8 (0.5–6.5)
593	Insulation workers	17/1,	180 (23.5–1375)
779	Machine operators, not specified	6/26,	2.0 (0.8–5.0)
869	Construction laborers	8/57,	1.7 (0.7–3.8)
Industries			
60	Construction	43/288,	1.7 (1.2–2.4)
192	Industrial and miscellaneous chemicals	4/15,	2.3 (0.7–7.0)
262	Miscellaneous non-metallic mineral and stone products	5/6,	7.6 (2.3–25.5)
312	Construction and material handling machines	3/10,	3.3 (0.9–12.4)
342	Electrical machinery, equipment, and supplies	6/12,	5.1 (1.8–13.9)
722	Services to dwellings and other buildings	3/9,	3.9 (1.0–14.8)
Women			
Occupations			
156	Teachers, elementary school	22/106,	1.5 (0.8–2.6)
407	Private household cleaners and servants	6/73	2.0 (0.6–6.5)
458	Hairdressers and cosmetologists	6/37,	1.7 (0.7–4.1)
779	Machine operators, not specified	6/25,	2.6 (1.0–6.3)
Industries			
172	Printing and publishing, except newspapers	5/14,	3.8 (1.3–10.8)
682	Miscellaneous retail stores	4/9,	5.0 (1.5–16.6)
772	Beauty shops	6/37,	1.7 (0.7–4.2)
842	Elementary and secondary schools	33/179,	1.5 (1.0–2.4)

RESULTS

Average age at death of peritoneal cancer cases was 64.3 $\pm$ 13.5 among men (64.3 $\pm$ 13.5 among Whites, and 64.8 $\pm$ 8.8 among African-Americans), and 70.1 $\pm$ 12.0 among women (70.2 $\pm$ 11.8 among Whites, and 67.2 $\pm$ 14.9 among African-Americans). Only 15.9% of male cases (36/226) and 7.7% of female cases (28/362) for whom information was available had autopsy, compared to 14.2% of male controls (269/1900) and 9.1% of female controls (266/2910). Seventeen male cases (6.8%) and one male control were reported as insulation workers in the death certificate (Table I). Machine operators also showed a risk increase in both genders, which was significant among men. Non-significantly elevated risks of peritoneal cancer were observed for mechanics and repairers and construction laborers among men, and elementary school teachers; private household cleaners and servants; and hairdressers and cosmetologists among women. Industries with a significant excess risk among men included construction; miscellaneous nonmetallic mineral and stone products; electrical machinery, equipment and supplies; and services to dwellings and other buildings. Industries associated with a significantly elevated risk among women were quite different and they included: publishing and printing, miscellaneous retail stores, and elementary and secondary schools.

Table II describes the results obtained with the job-exposure matrix. Risk of peritoneal cancer increased significantly by probability (test for trend: all men: $p = 0.0004$; white men $p = 0.016$) and intensity (test for trend: all men: $p = <0.0001$; white men $p = 0.0006$) of exposure among all men and white men. A significant upward trend was also observed among African-American men by intensity of

TABLE II. ORs for Peritoneal Cancer by Probability and Intensity of Exposure to Asbestos: Study of Death Certificates in 24 U.S. States, 1984–1992

	Whites		African-Americans		All	
Exposure metric	**Cases/ controls**	**OR (95% C.I.)**	**Cases/ controls**	**OR (95% C.I.)**	**Cases/ controls**	**OR (95% C.I.)**
Men						
Probability of exposure						
Baseline	159/1,661	1.0 —	8/114	1.0 —	167/1,775	1.0 —
Low	17/172	1.1 (0.6–1.9)	3/12	3.9 (0.8–19.0)	20/184	1.2 (0.8–2.0)
Medium	38/474	0.9 (0.6–1.4)	7/54	2.3 (0.7–7.5)	45/528	1.0 (0.7–1.5)
High	17/3	60.0 (17.1–211)	0/0	— —	17/3	61.6 (17.5–216)
Test for trend (p value)		0.0016		0.15		0.0004
Intensity of exposure						
Baseline	159/1,661	1.0 —	8/114	1.0 —	167/1,775	1.0 —
Low	20/288	0.8 (0.5–1.4)	2/30	1.3 (0.2–7.5)	22/318	0.9 (0.5–1.4)
Medium	31/320	1.1 (0.7–1.6)	7/29	3.6 (1.1–12.0)	38/349	1.3 (0.9–1.8)
High	21/41	5.1 (2.9–9.1)	1/7	2.7 (0.3–27.4)	22/48	4.8 (2.8–8.3)
Test for trend (p value)		0.0006		0.04		0.0000
Women						
Probability of exposure						
Baseline	369/3,655	1.0 —	17/175	1.0 —	386/3,830	1.0 —
Low	4/20	2.5 (0.8–7.5)	0/2	— —	4/22	2.2 (0.7–6.6)
Medium	15/205	0.7 (0.4–1.3)	3/23	2.2 (0.5–10.3)	18/228	0.8 (0.5–1.4)
Likely	0/0	— —	0/0	— —	0/0	— —
Test for trend (p value)		−0.75		0.91		−0.48
Intensity of exposure						
Baseline	369/3,655	1.0 —	17/175	1.0 —	386/3,830	1.0 —
Low	12/185	0.7 (0.4–1.3)	3/20	2.8 (0.6–14.2)	15/205	0.8 (0.4–1.4)
Medium	7/40	2.0 (0.9–4.6)	0/5	— —	7/45	1.8 (0.8–4.1)
High	0/0	— —	0/0	— —	0/0	— —
Test for trend (p value)		0.33		0.27		0.40

asbestos exposure ($P = 0.04$), although the trend was not monotonic. No African-American men had high probability of exposure. Risk of peritoneal cancer did not increase with probability of asbestos exposure among women, although no female cases had high probability of exposure. Risk was non-significantly elevated in the medium intensity of exposure for all women and white women. Among women, trends were not statistically significant, and the highest risk was observed for moderate intensity of exposure to asbestos. However, it was modest and not significant. Also, among women, neither cases nor controls were assigned to high probability or intensity of exposure to asbestos. Seventeen male cases and three controls had high probability of exposure to asbestos, which was therefore associated with a 62-fold increase in risk of peritoneal cancer. All were white men. Although our matrix classified other occupations in the high probability of exposure, the excess was entirely driven by insulators. Most insulators worked in the construction industry (13/17), two in electric utility companies, and one each in manufacturing of industrial chemicals and in an unspecified manufacturing industry. Among other occupations in the construction industry, risk was not elevated for supervisors and carpenters, and small non-significantly elevated risks were observed for construction laborers and painters (OR = 1.3, not shown in Table I). A fivefold increase in risk was associated with high intensity of exposure to asbestos. Cross-classification of study subjects by exposure probability and intensity did not add much further information, because of small numbers and empty cells.

DISCUSSION

Our results confirm that occupational exposure to asbestos is associated with a very high risk of peritoneal cancer. Insulators showed the highest risk, and they contributed the most to the significant increase in risk in the construction industry. However, elevated risks were also observed for machine operators in both genders, in a few manufacturing industries, and among workers employed in services to dwellings and other buildings. The test for trend was significant either by probability or by intensity of exposure to asbestos. Among women, risk was elevated in the publishing and printing industry, in retail stores, and in elementary and secondary schools. Trends by probability and intensity of exposure to asbestos were not significant.

As Selikoff pointed out (Selikoff, 1992a), the finding of new high-risk groups for asbestos-related diseases in studies based on death certificates should be explained with the tendency to list the most recent occupation in the death certificate, while prior or short-term asbestos work would not be expected to be recorded. This might account for most of the positive findings among women in the present study, such as elementary and secondary schools. Our matrix classified teachers in the reference category, although asbestos was widely used for insulation purposes in schools. In fact, as explained in the Methods section, our unexposed reference group also included subjects with low probability and low intensity exposure. However, cases of pleural mesothelioma among teachers have been discussed in relation to their asbestos exposure in school buildings [Lilienfeld, 1991; Anderson et al., 1991], and a history of prior employment in other occupations and industries with probable asbestos exposure was positive only for 3/12 teachers and 5/29 maintenance workers who died from mesothelioma in Wisconsin [Anderson et al., 1991]. It has been suggested that environmental, possibly residential, exposure to asbestos may account for the majority of female peritoneal mesotheliomas [Dawson et al., 1993]. Spouse exposure was reported as a risk factor for mesothelioma among women in England and Wales [Greenberg and Lloyd Davies, 1974]. Unfortunately, we did not have information on spouse occupation to explore whether a greater proportion of women in the occupations and industries with an increase in peritoneal cancer risk were married to blue collar workers, which might also have explained some of our findings among women. Therefore, difficulties in identifying precisely the sources of exposure to asbestos and the possibility that other causative agents are involved [Peterson et al., 1984], warrant a conservative evaluation for most positive findings on peritoneal cancer and occupation among women. On the other hand, the hypothesis of an association for female teachers and other workers in elementary and secondary schools cannot be discarded in light of previous reports of pleural mesothelioma cases among these workers.

Spirtas et al. calculated a relative risk (RR) of 3 (95%CI 0.7,16.5) for peritoneal mesothelioma associated with having ever held any of nine activities where asbestos exposure was suspected, based on 20 male cases and 203 controls [Spirtas et al., 1994]. By applying the same criteria to define exposure to asbestos, we obtained an OR of 1.8 (95%CI 1.3,2.4) among men in our study. Therefore, results from our job-exposure matrix are consistent with Spirtas et al. The lower risk in the present study may have resulted from the exposure misclassification related to the availability of information on the sole occupation and industry reported on the death certificate, compared to lifetime work histories obtained with telephone interview in the cited paper, and to the disease misclassification due to the use of death certificate diagnoses instead of histopathology data.

Workplace environments typically involve exposure to a complex mixture of physical and chemical agents, each of which might be responsible for an observed association. Compared to occupation and industry titles only, using job-exposure matrices in epidemiologic analyses offers the advantages of a clearer definition of the risk factor and of a greater statistical power by assembling subjects with the same exposure in various occupations and industries. However, level of detail in the occupation and industry coding system and completeness in working histories of study subjects are critical factors for the performance of job-exposure matrices in identifying the exposure of interest [Dosemeci et al., 1994]. In the 24 states death certificates database, only one occupation and industry are registered. These are coded with the 3-digit 1980 U.S. Census code, which may not be specific enough in discriminating among exposed and unexposed subjects. The resulting non-differential misclassification would bias the risk estimate toward the null. These disadvantages are more important in studies involving women, as the reliability of the occupational information in death certificates is poorer for women than men [Schade and Swanson, 1988]. Therefore, negative findings should be interpreted with caution.

A further obstacle in detecting associations based on death certificate information is related to disease misclassification. Not all deaths ascribed to cancers of the pleura or the peritoneum in the death certificates are mesotheliomas, and some mesotheliomas are misclassified to other sites [Ribak et al., 1989]. In his detailed review of the use of death certificates to detect occupational associations with asbestos exposure, Selikoff pointed out that due to a very poor sensitivity (20–23% in the United States, 32–51% among asbestos insulators), the use of standard death registrations vastly underestimate the incidence of mesothelioma [Selikoff , 1992b; Selikoff and Seidman, 1992]. However, the specificity of the death certificate diagnosis of peritoneal mesothelioma among asbestos iInsulation workers was very high as all 92 cases so indicated were confirmed after best evidence procedures [Selikoff and Seidman, 1992]. Also, no major differences in diagnostic accuracy were found by comparing diagnosis of mesothelioma in death certificates of asbestos insulation workers and former non-unionized asbestos factory workers, whose death certificate had virtually no indication of occupational exposure to asbestos [Selikoff, 1992a]. In our study, we had available only the ICD-9 code and not the original certificate, which means that we were unable to discriminate mesothelioma from the rest of peritoneal cancers. Therefore, specificity in detecting mesothelioma was also lowered in our study.

Nonetheless, the observed strong association between asbestos and peritoneal cancer in men provides evidence that information on cause of death and usual occupation and industry on the death certificate is reliable. In addition, the results of this study suggest that using job-exposure matrices is an appropriate approach in a first-step evaluation of occupational carcinogens with the case-control design. The use of histopathologic data to define cases and a careful evaluation of complete work and residential history are of paramount importance in evaluating whether other risk factors besides occupational exposure to asbestos are involved in the etiology of peritoneal mesothelioma among women.

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